ADVM-022 (ixoberogene soroparvovec) Intravitreal Gene Therapy for Neovascular Age-Related Macular Degeneration: End of Study Results from the 2-Year OPTIC Trial

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– On behalf of the OPTIC investigators –

OPTIC
Gene Therapy in nAMD

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Disclosures

- Research Support-Wills Retina Service
  - **Adverum**, Allergan, Annexon, Apellis, Astellis, Eyepoint, Genentech, Graybug, Gyroscope, Iveric, Kodiac, Lineage, NGM, Notal, Novartis, Ocugen, Opthea, Regeneron, RegenXBio
- Consulting
  - 4DMT, **Adverum**, Allergan, Annexon, Apellis, Clearside, Eyepoint, Genentech, Graybug, Iveric, Janssen, Kodiac, Lineage, Merck, NGM, Novartis, Ocugen, RegenXBio, Stealth, Thea, Zeiss

OPTIC Study: 2-Year Safety and Efficacy of ADVM-022 for nAMD

OPTIC Gene Therapy in nAMD

Primary Objective

- Assess the safety and tolerability of a single IVT injection of ADVM-022

Secondary Objective

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6 wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA (ETDRS) from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

**Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.*
Final analysis includes all participants regardless of baseline neutralizing antibody titer.
AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

Final 2-Year Analysis

ADVM-022 OPTIC Study Baseline Characteristics

Baseline Characteristics	Cohort 1 $6x10^{11}$ (N=6)	Cohort 2 $2x10^{11}$ (N=6)	Cohort 3 $2x10^{11}$ (N=9)	Cohort 4 $6x10^{11}$ (N=9)
Mean (range) Age, Years	79.0 (62–88)	79.8 (74–90)	77.4 (65–90)	79.9 (68–88)
Mean (range) Years Since nAMD Diagnosis	4.5 (0.9–10.6)	4.1 (0.5–6.8)	3.3 (0.7–8.0)	3.2 (0.2–8.0)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis*	38.2 (7–109)	34.0 (4–69)	24.8 (9–70)	28.5 (2–58)**
Mean (range) Annualized anti-VEGF Injections Prior to ADVM-022	9.7 (8.4–11.2)	10.5 (8.5–11.7)	9.6 (7.9–12.8)	9.9 (6.3–13)**
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.8 (57–77) 20/50	64.7 (53–72) 20/50	65.9 (53–75) 20/50	65.0 (54–77) 20/50
Mean (range) CST, µm	369.2 (293–561)	307.7 (235–339)	473.4 (301–857)	398.6 (255–538)

**Not including the mandated aflibercept at Screening; **Excluding participant #2 with incomplete prior anti-VEGF data;*
BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NAbs, neutralizing antibodies; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

Final 2-Year Analysis

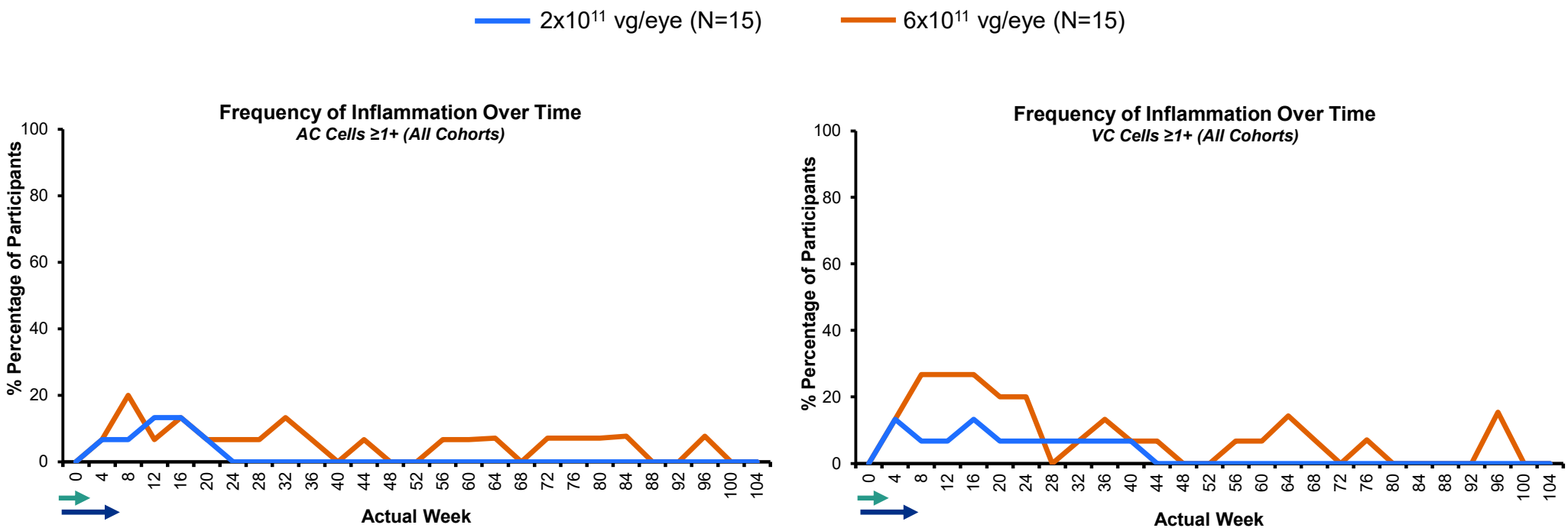
ADVM-022 OPTIC Study Safety Summary

- Despite the short duration of prophylactic corticosteroid therapy, ADVM-022 was generally well tolerated, with the most common AE of dose-dependent, mild to moderate* inflammation that was responsive to topical corticosteroids
  - At study completion, inflammation in the $2x10^{11}$ dose group resolved in all participants and no participants required corticosteroid therapy
- Across all cohorts, most ADVM-022-related ocular AEs were mild (83.7%) to moderate (15.6%)
- The most commonly reported ocular AE was anterior chamber cell
- Two ADVM-022 related SAEs were reported: uveitis (responsive to topical corticosteroids) and dry AMD
- No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- No clinically relevant low IOP events observed at either dose

AC, aqueous cells; AE, adverse event; SAE, serious adverse event; VC, vitreous cells.
**Mild inflammation: trace, 0.5+, 1+ and 2+ anterior chamber cell/flare, or trace, 0.5+, 1+ and 2+ vitreous cells; moderate inflammation: +3 anterior chamber cell/flare, or 3+ vitreous cells; severe inflammation: +4 anterior chamber cell/flare, or 4+ vitreous cells*

Final 2-Year Analysis

Lower Immune Response with ADVM-022 2x10^{11} vg/eye

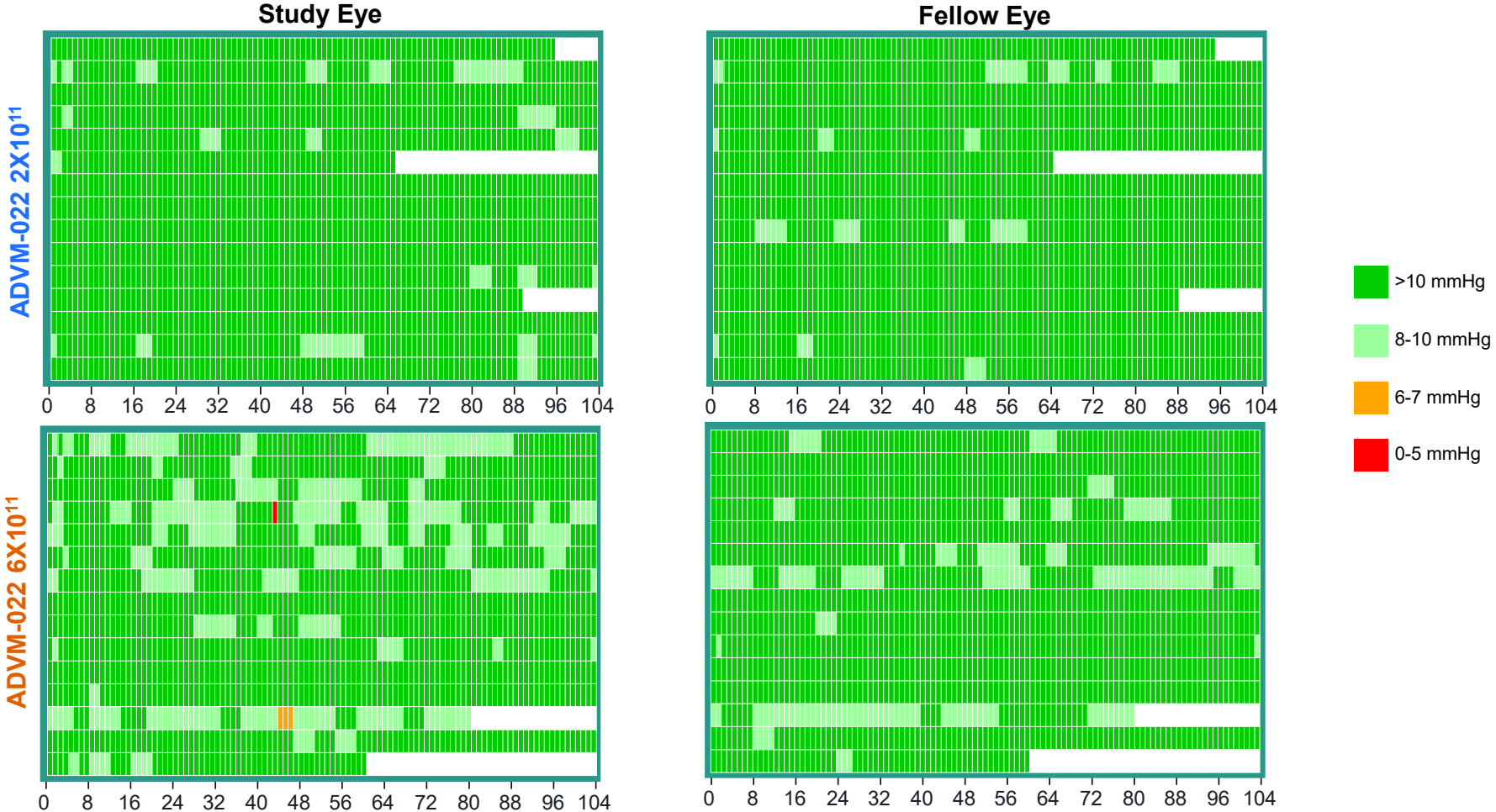


Corticosteroid prophylactic regimen: 13 days oral prednisone or 6 weeks of topical drops

AC, aqueous cells; VC, vitreous cells.
Cell grades as assessed by slit lamp, Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health guidelines for vitreous cells.
AC: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells; VC: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; Rare cells are captured as 0.5+ for this analysis

Final 2-Year Analysis

Comparable IOP Observed Between Study and Fellow Eyes in the 2x10^{11} Dose Group Through 2 Years - No Hypotony in Either ADVM-022 Dose Group

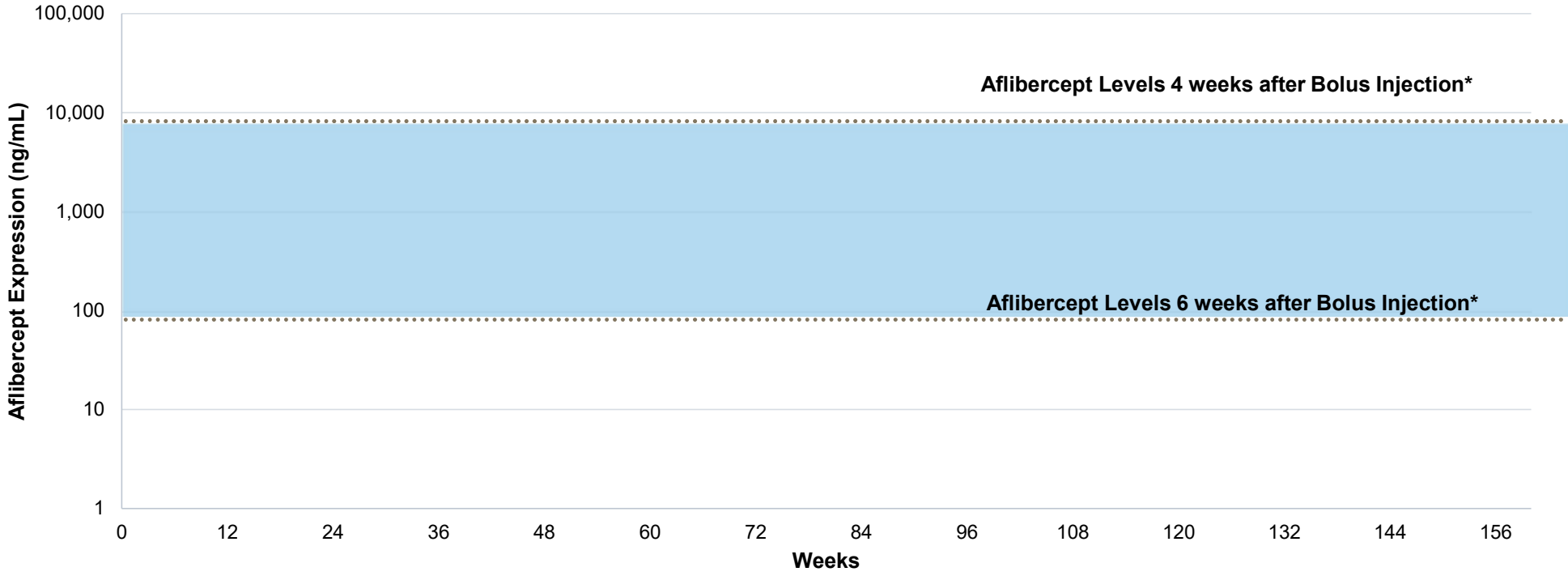


IOP decrease in 6x10^{11} dose group at Week 44 due to retinal detachment

Final 2-Year Analysis

ADVM-022: Continuous Therapeutic Aflibercept Expression Comparable to Bolus Aflibercept 4-6 weeks Post Injection

Individual Participant Plots



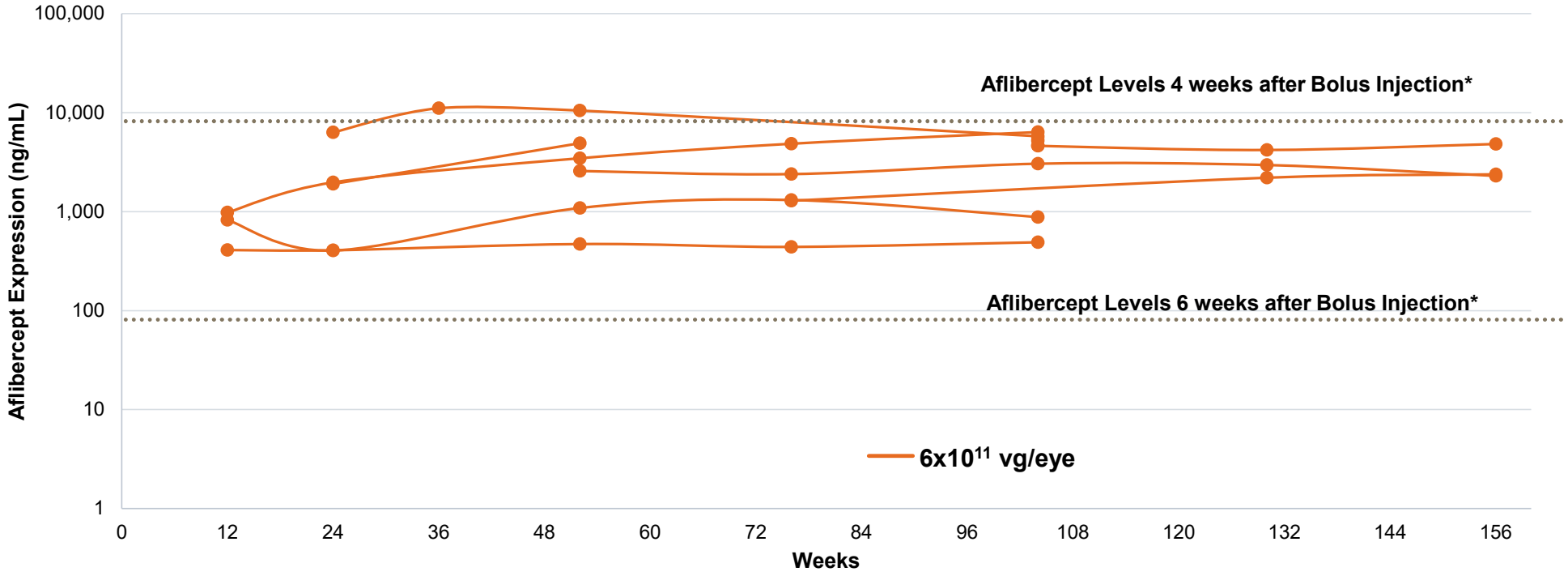
*Modeled based on Do et al. Retina 2020; 40:643-647.

Protocol amendment for aqueous sample collection for participants that consented.

To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

ADVM-022: Continuous Therapeutic Aflibercept Expression Levels Sustained Through 3 Years

Individual Participant Plots – $6x10^{11}$ Dose Group



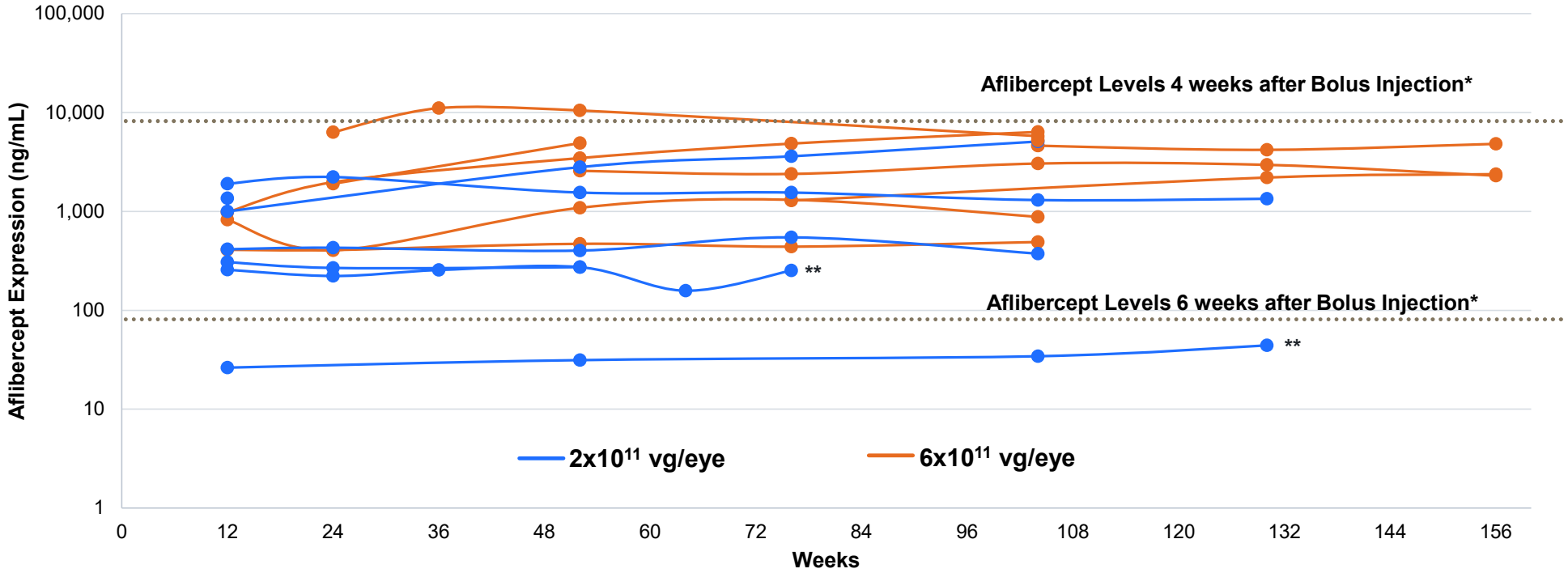
*Modeled based on Do et al. Retina 2020; 40:643-647.

Protocol amendment for aqueous sample collection for participants that consented. No samples available from Cohort 2.

To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

ADVM-022: Comparable Therapeutic Aflibercept Levels with Both Doses - Sustained Through 3 Years

Individual Participant Plots – $2x10^{11}$ Added



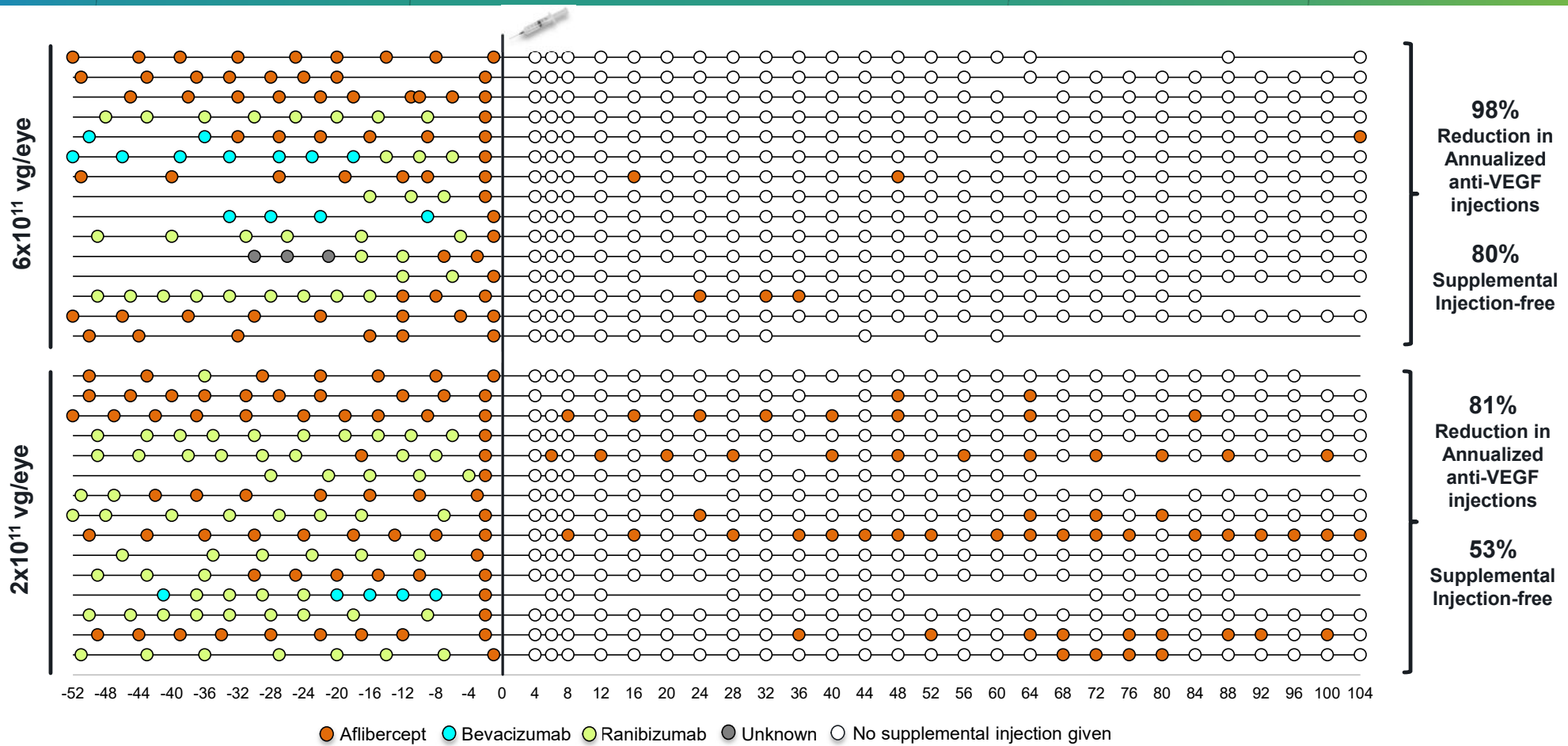
*Modeled based on Do et al. Retina 2020; 40:643-647.

** Participant received supplemental aflibercept injections

Protocol amendment for aqueous sample collection for participants that consented. No samples available from Cohort 2.

To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

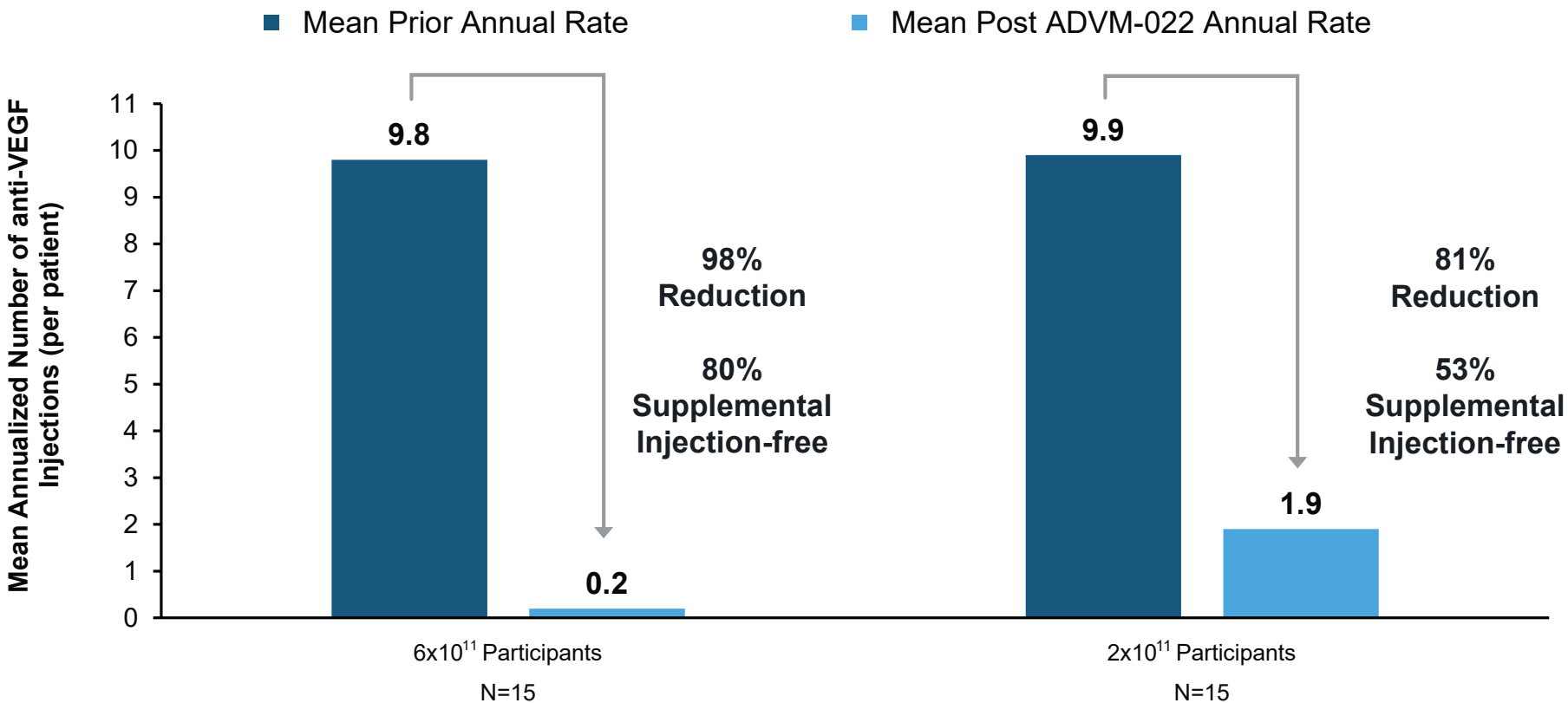
Reduction in Supplemental Aflibercept Injections Following ADVM-022



Six patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 1, 2 and 3, three in Cohort 4. Cohort 2, Patient 1 death due to cardiopulmonary arrest due to hypoxia; Cohort 2, Patient 6 death due to lung malignancy; Incomplete prior data for Cohort 4, Patient 2. Cohort 4, Patient 4 had a port delivery system (PDS) implanted 3 years prior to Screening (explanted 1.5 years later); Cohort 4, Patient 5 received in a clinical trial not yet unmasked (NCT03790852); IVT, intravitreal injection

Final 2-Year Analysis

81-98% Reduction in Annualized Anti-VEGF Injections Following a Single ADVM-022 IVT Injection



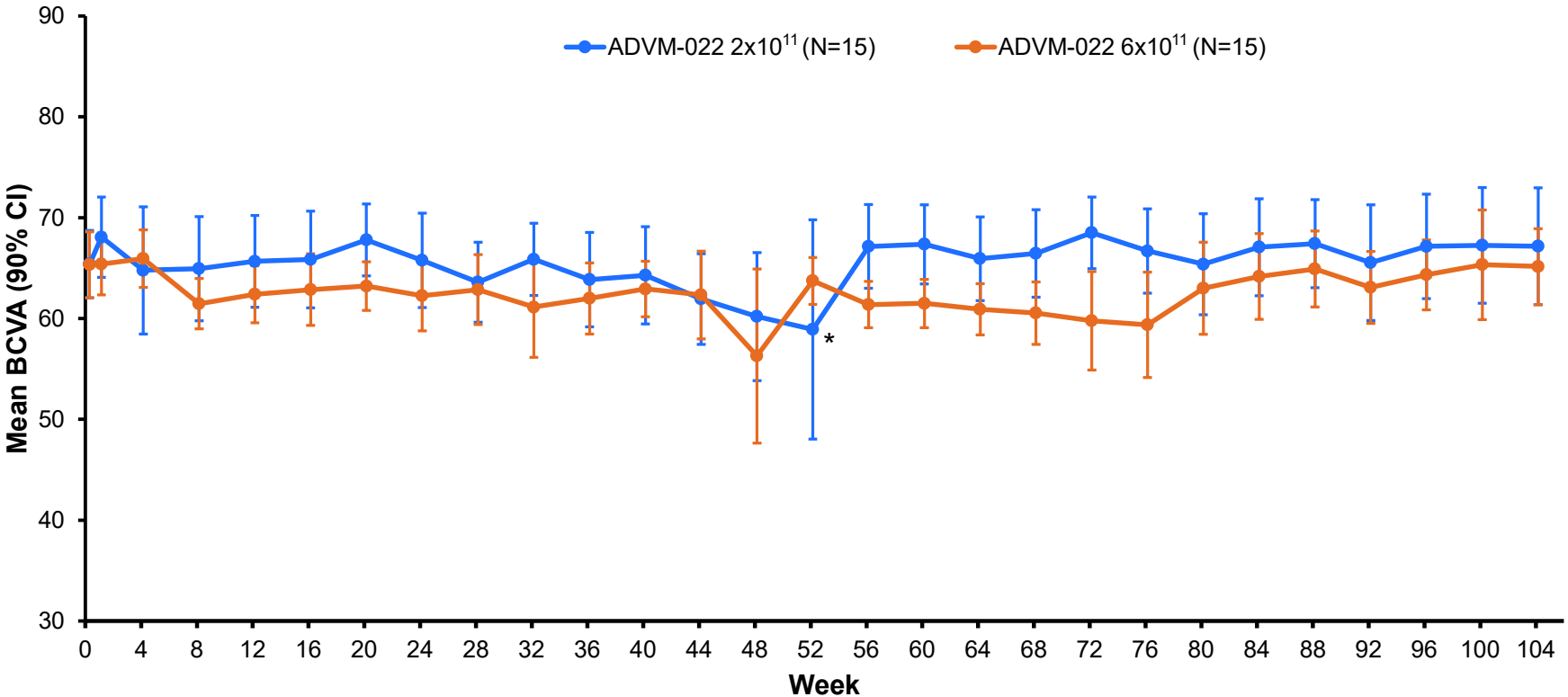
Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).
All participants included in analysis regardless of baseline neutralizing antibody titer.
VEGF, vascular endothelial growth factor.

Final 2-Year Analysis

BCVA Maintained Over Time With Both ADVM-022 Doses

OPTIC Gene Therapy in nAMD

Mean BCVA (90% CI) by Cohort and Week



Mean BCVA (letters) change from baseline to last visit (90% CI)

+0.2 (-4.6, 5.0)
2x10^11 vg/eye

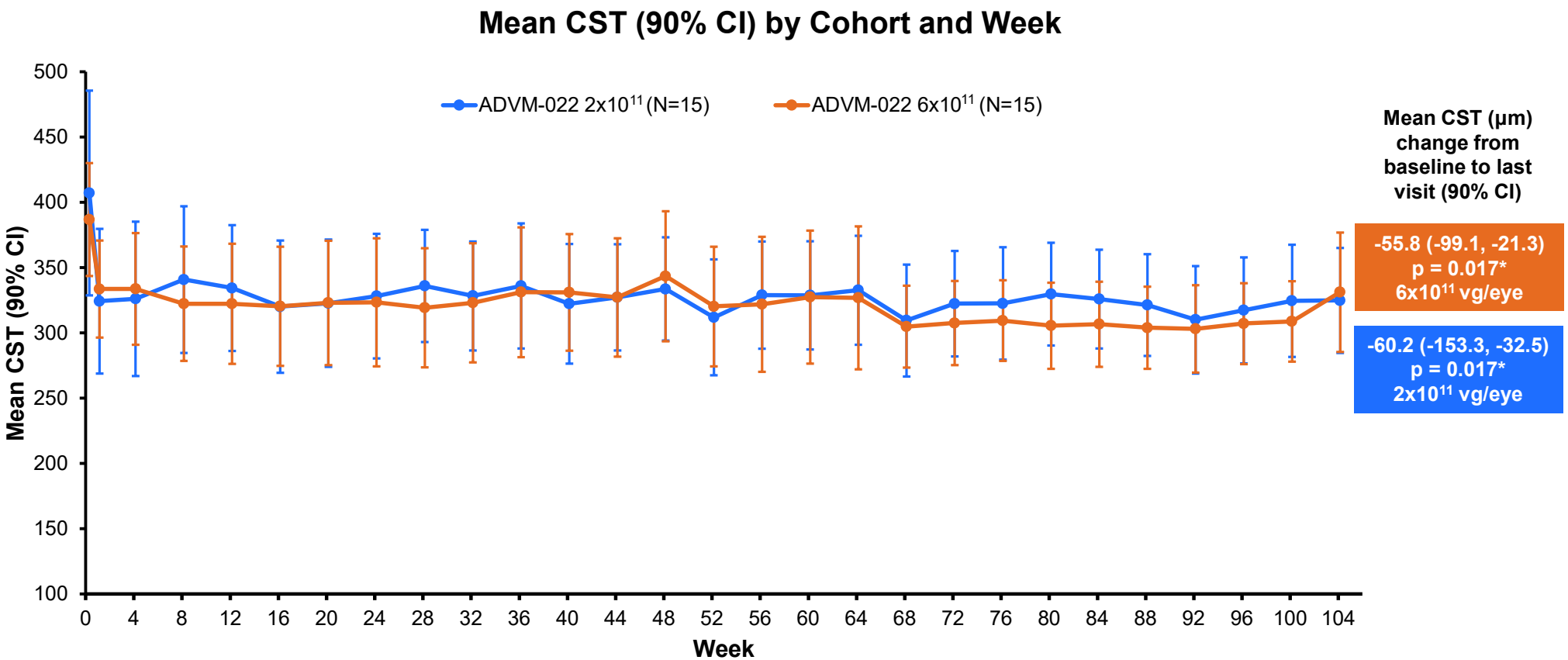
-0.4 (-3.5, 2.7)
6x10^11 vg/eye

p = 0.855**

**Cataract surgery*
***Derived from a two-sample t-test.*

Final 2-Year Analysis

Mean CST Significantly Reduced With Both ADVM-022 Doses

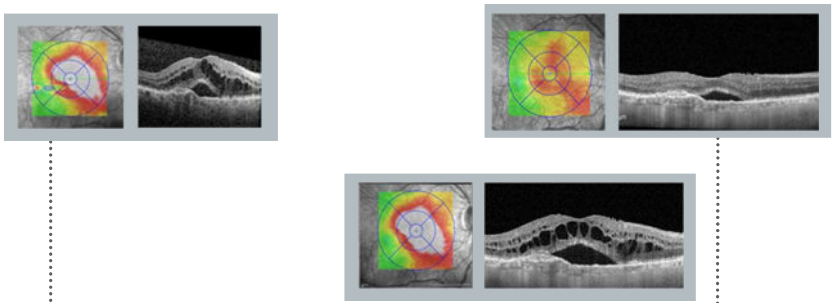


*Derived from a two-sample t-test.

Final 2-Year Analysis

ADVM-022 Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections Out to 104 Weeks

Cohort 3 ($2x10^{11}$ vg/eye) Participant

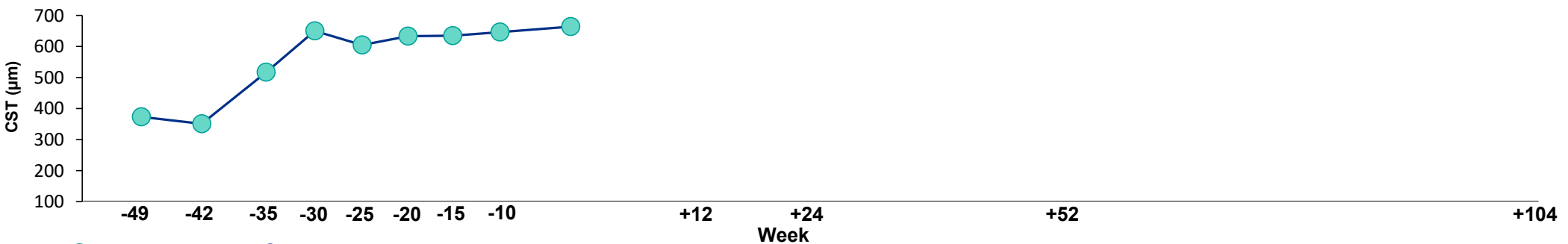


Persistent fluid despite frequent anti-VEGF injections

-30 wks

-2 wks (baseline)
BCVA: 75 letters
CST: 664 µm

Treatment with aflibercept Q5W

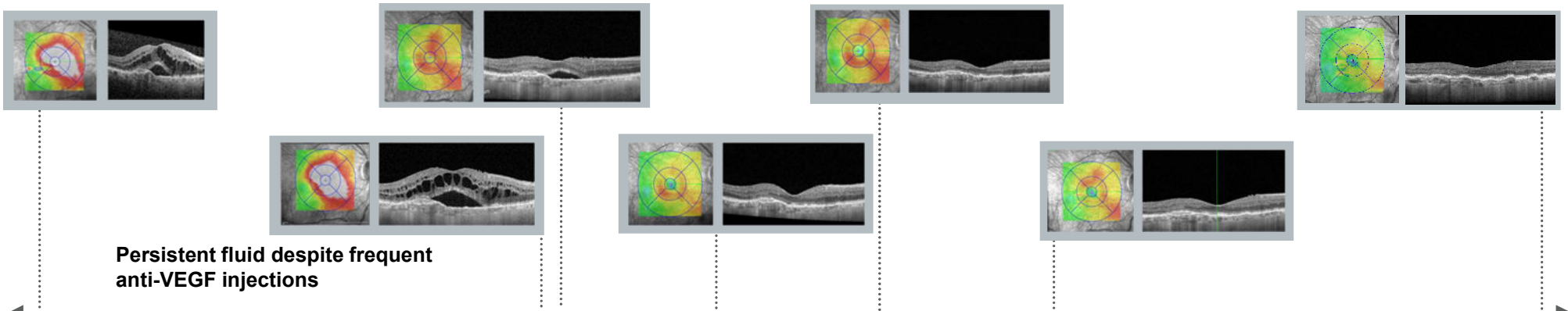


Final 2-Year Analysis

ADVM-022 Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections Out to 104 Weeks

OPTIC Gene Therapy in nAMD

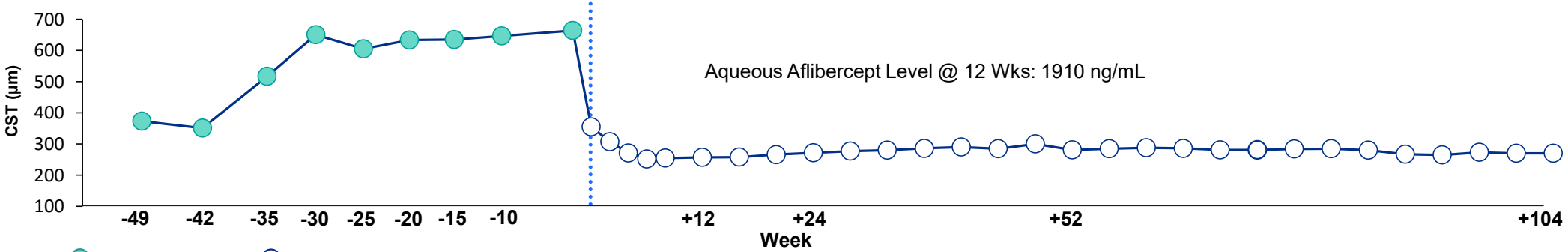
Cohort 3 ($2x10^{11}$ vg/eye) Participant



Persistent fluid despite frequent anti-VEGF injections

-30 wks	-2 wks (baseline)	Day 0	+12 wks	+24 wks	+52 wks	+104 wks
	BCVA: 75 letters	ADVM-022	BCVA: +6 letters	BCVA: +8 letters	BCVA: +8 letters	BCVA: +9 letters
	CST: 664 µm		CST: -407 µm	CST: -392 µm	CST: -383 µm	CST: -394 µm

Treatment with aflibercept Q5W



Final 2-Year Analysis

ADVM-022 OPTIC Study Conclusions

- ADVM-022 was generally well tolerated. Mild to moderate inflammation was the most common adverse event, which was dose-related and responded to topical corticosteroids
    - All participants who received ADVM-022 $2x10^{11}$ vg/eye dose were inflammation free and did not require corticosteroids at the end of the study
- A single IVT injection of ADVM-022 resulted in sustained therapeutic aflibercept expression through at least 3 years. An extension study will follow-up subjects out to 5 years.
- Mean annualized anti-VEGF injections were reduced by 81-98% in all participants, and majority of participants (53%) in $2x10^{11}$ vg/eye dose groups were supplemental injection free over two years
- BCVA and CST were maintained or improved through two years with both doses
- The $2x10^{11}$ dose demonstrated a favorable benefit/risk profile despite short duration corticosteroid prophylaxis, warranting further development for treatment of nAMD
    - The ongoing Phase 2 LUNA study is evaluating the $2x10^{11}$ vg/eye dose, as well as a new, lower $6x10^{10}$ vg/eye dose, combined with enhanced prophylactic corticosteroid regimens in patients with nAMD

Final 2-Year Analysis

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